

Exhibit 18

Risk Factors for Ovarian Carcinoma

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KEYWORDS

- Ovarian cancer • Risk factors • Descriptive epidemiology • Risk reduction
- Tumor heterogeneity

KEY POINTS

- Ovarian cancer continues to be the leading gynecologic killer of women in the United States.
- Most women present with advanced-stage disease at time of diagnosis and there are currently no effective screening strategies for average-risk women.
- Cancer epidemiology greatly contributes to the understanding of factors that may modify disease development and drive tumor heterogeneity.

INTRODUCTION

Ovarian cancer is the second most common gynecologic malignancy overall worldwide and the most lethal gynecologic malignancy in the United States and Europe. Each year, approximately 200,000 women worldwide are diagnosed with ovarian cancer and approximately 125,000 women die from the disease.¹ Most patients present with advanced-stage disease because symptoms of early-stage disease may be subtle or generalized.² Standard treatment of advanced ovarian cancer involves cytoreductive surgery in combination with taxane-platinum-based chemotherapy.¹ However, most patients experience recurrence and eventually succumb to their disease even with optimal initial treatment.³

Given this, identifying risk factors, preventive strategies, and high-risk populations is crucial. However, epidemiologic studies face several challenges. First, ovarian cancer is rare. Furthermore, because ovarian cancer is a heterogeneous disease, considering

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outcomes of specific cancer subtypes is critical to provide clues to underlying mechanisms. As a result, it is crucial to have large sample sizes to ensure power. Thus, several consortia have been initiated to pool resources from multiple studies and conduct investigations that would not be possible in any single study. Pooling studies that span different time periods further allows addressing a second challenge, which is the temporal changes in clinical characterization of ovarian cancer and changes in certain exposures (eg, oral contraceptive pill [OCP] doses) over time.

Importantly, removal of the ovaries and fallopian tubes reduces risk by up to 80% to 90%.⁴ However, negative health consequences, including cardiovascular mortality,^{5,6} necessitate the use of this procedure only among high-risk women who would have a net benefit, such as those with *BRCA* or other high-penetrance mutations. However, in average-risk women, efforts to develop well-calibrated risk prediction models have been largely unsuccessful, with low predictive capability even when using known ovarian cancer risk factors (area under the curve [AUC], 0.59–0.64).^{7–10} Addition of low-penetrance alleles only modestly improved the AUC to 0.66,¹¹ requiring identification of new risk factors.¹² A potential reason for the low predictive ability is ovarian cancer heterogeneity, necessitating consideration of subtype-specific risk factor associations. The focus of this article is to review risk factor associations by tumor subtypes to inform the future research that is needed to improve risk prediction.

NONEPITHELIAL OVARIAN CANCER RISK FACTORS

A small proportion of ovarian tumors are from a nonepithelial origin and generally have not been considered in risk modeling efforts. Specifically, sex-cord stromal ovarian neoplasms represent only 1.2% of ovarian cancer cases. These tumors are diagnosed at earlier stages and younger ages, in sharp contrast with epithelial ovarian cancer.¹³ Limited data suggest that nonwhite, obese women with a family history of breast or ovarian cancer are at increased risk for this subtype. *BRCA* germline mutations or a genetic predisposition to breast cancer are not related,¹⁴ although germline mutations in *DICER1*¹⁵ and somatic mutations in *FOXL2* are related to these tumors.¹⁶ Ovarian germ cell tumors account for 5% of malignant ovarian neoplasms,¹⁷ with early stage at younger ages.¹⁸ The incidence increases around puberty.¹⁹ There is a greater incidence among Asian/Pacific Islander and Hispanic women than in white women.²⁰ No definite genetic abnormalities have been identified in families with germ cell tumors.

EPITHELIAL OVARIAN CANCER RISK FACTORS

Epithelial ovarian cancer comprises greater than 90% of malignant epithelial neoplasms and often is diagnosed in postmenopausal women. Incidence is higher in white women (12.8 per 100,000) than in black women (9.8 per 100,000).²¹ Incidence seems to be lowest for American Indians/Alaska Natives. Incidence has been declining, with a 1.6% decrease in incidence and 2.1% decrease in mortality per year from 2003 to 2012 in the United States.²²

Many traditional ovarian cancer risk factors are reproductive or hormonal. In general, processes that decrease the number of ovulatory cycles are protective. For example, OCP use, multiparity, breastfeeding, and tubal ligation, as well as late age at menarche and early age at menopause, have been consistently associated with decreased risk, many with a dose-response relationship.²² However, studies among women using more recent lower-dose OCP formulations do not observe a decreased risk except with very long durations of use (>10 years).^{23–25} Further, use of hormone therapy, including unopposed estrogen and combined estrogen and progestin, seems

to increase risk.^{26–31} Other risk factors include endometriosis, taller height, and high body mass index in adolescence.^{32–36}

Variation in Risk Associations according to Ovarian Cancer Subtypes

Ovarian cancers represent a diverse group of diseases that are unique based on precursor lesions, histology, cause, developmental origins, as well as distinct mutational profiles.^{37,38} Stratification based on subtypes is critical for understanding mechanisms underlying risk factor associations and for developing improved risk prediction models. Although the most common assessment of heterogeneity is based on histologic subtypes (ie, the morphologic features of the tumor) and grade, other metrics have also been used. Large-scale studies that examined risk factors for specific ovarian cancer subtypes are summarized later.

Histologic subtypes

Unexpectedly, most known ovarian cancer risk factors show stronger associations with nonserous tumors, which comprise ~25% of epithelial ovarian cancers, than the more aggressive serous tumors ([Table 1](#)). For example, in a pooled analysis of 21 prospective cohort studies in the Ovarian Cancer Cohort Consortium (OC3), reproductive risk factors, including lower parity and older age at menopause, as well as endometriosis, were associated primarily with increased risks of endometrioid and clear cell tumors.³¹ This finding is consistent with pooled analyses of case-control studies and studies of endogenous hormones.^{39,40} Notably, OCP use seems equally protective across histologic subtypes in multiple studies.^{31,39} Surgical procedures, including tubal ligation and hysterectomy, also seem to primarily decrease the risk of nonserous tumors.^{31,41–44} Data on histologic subtype-specific associations for salpingectomy are currently unavailable, because few studies have examined this association and most have had few exposed cases.^{31,42,43}

Associations of several lifestyle factors and use of over-the-counter medications with risk of specific ovarian cancer histologic subtypes have also been investigated. Smoking was associated with an increased risk of mucinous ovarian tumors but a decreased risk of clear cell tumors in several studies.^{31,45} A pooled analysis of 8 case-control studies found modest increases in risks of serous, endometrioid, and clear cell carcinomas, but not mucinous tumors, in women who used genital talc powder.⁴⁶ Aspirin and other nonsteroidal antiinflammatory drug use was mainly associated with serous disease in both prospective and retrospective consortial analyses.⁴⁷ Similarly, history of ovarian cancer is one of the few factors that is more strongly associated with serous carcinoma.³¹ Family history of breast cancer was most strongly related to endometrioid tumors.

Multiple studies have integrated grade and histologic subtype to evaluate associations for high-grade and low-grade serous tumors separately because these are thought to have different causes.^{31,42,43} In general, low-grade serous tumors had similar associations to endometrioid and clear cell disease, although family history of ovarian cancer was related to high-grade serous tumors.³¹ A key caveat in these studies is that grade does not have standard classification criteria and is often missing in epidemiologic studies, reducing power and leading to misclassification of disease subtype.

Biologically, these results support the theories of differing cells of origin in ovarian cancer, notably with endometriosis and tubal ligation being strongly associated with histologic subtypes thought to be directly linked with endometriotic tissue and retrograde menstruation.⁴⁸ Similarly, the family history of ovarian cancer relationship with high-grade serous disease is likely explained in part via BRCA mutations. In the

Table 1 Summary of putative cells of origin and identified risk factors for specific ovarian cancer histologic subtypes			
Subtype	Putative Cells of Origin	Reproductive and Hormonal Risk Factors	Family History, Demographic, and Lifestyle Risk Factors
All serous	Ovarian surface epithelium, fallopian tube epithelium	Lower parity ^{31,39} Shorter duration of OC use ^{31,39} HT use/longer duration of use ^{31,39} No history of tubal ligation ^{42–44}	Family history of breast cancer ³¹ Family history of ovarian cancer ³¹ Taller height ³¹ Genital powder use ⁴⁶ No regular aspirin use ⁴⁷
High-grade serous	Ovarian surface epithelium, fallopian tube epithelium	Lower parity ³¹ Shorter duration of OC use ³¹ Longer duration of HT use ³¹ No history of tubal ligation ^{42,43}	Family history of ovarian cancer ³¹ Taller height ³¹
Low-grade serous	Ovarian surface epithelium, fallopian tube epithelium	Lower parity ³¹ Shorter duration of OC use ³¹ Longer duration of HT use ³¹	—
Endometrioid	Endometriosis	^a Lower parity ^{31,39} Shorter duration of OC use ^{31,39} HT use/longer duration of use ^{31,39} ^a Older age at menopause ^{31,39} ^a No history of tubal ligation ^{31,42–44} Endometriosis ³¹	^a Family history of breast cancer ³¹ Taller height ³¹ Genital powder use ⁴⁶
Clear cell	Endometriosis	^a Lower parity ^{31,39} Shorter duration of OC use ^{31,39} Shorter duration of HT use ³¹ ^a Older age at menopause ^{31,39} ^a No history of tubal ligation ^{31,42,43} No history of hysterectomy ³¹ Endometriosis ³¹	Taller height ³¹ Never smoking ³¹ Genital powder use ⁴⁶
Mucinous	Unknown	Lower parity ^{31,39} No history of tubal ligation ⁴²	Taller height ³¹ More pack-years ^{31,45}

Abbreviations: HT, postmenopausal hormone therapy; OC, oral contraceptive.
^a Indicates that the risk factor was most strongly related to this subtype(s).

OC3 analysis, unstructured hierarchical clustering suggested that few known risk factors were associated with serous tumors compared with endometrioid and clear cell diseases, which had very similar risk factor profiles.³¹ This finding is in stark contrast with breast cancer, for which risk factors for the most common type of tumor (estrogen receptor positive) are well understood, and may explain the poor predictive ability of prior risk models. Focusing on the risk factors that have been identified for serous disease may open up new areas of research to identify novel risk factors to best identify high-risk women and elucidate novel risk-reduction strategies.⁴⁹

Type 1 versus type 2

An additional method of classifying ovarian cancer subtypes groups certain histologic subtypes together based on putative cells of origin and somatic mutations and has been used in risk factor studies to enhance power.⁵⁰ Type 1 cancers consist of low-grade serous, endometrioid, clear cell, and mucinous cancers arising from the ovarian

epithelium or endometriosis and are characterized by mutations in *KRAS*, *ARID1A*, *PIK3CA*, *PTEN*, and *BRAF*. Type 2 cancers, which comprise high-grade serous cancers, carcinosarcomas, and undifferentiated carcinomas, are characterized by *TP53* mutations and likely originate from the distal end of the fallopian tube. In general, these studies have observed similar associations to those described earlier when looking at the finer granularity of histologic subtype and grade. For example, reproductive factors such as parity and tubal ligation were most strongly associated with a lower risk of type 1 tumors, whereas OCP use was consistently associated with a lower risk across both types.^{39,51,52}

Anatomic site

Research on ovarian cancer has historically encompassed primary ovarian, primary peritoneal, and primary fallopian tube cancers. However, several studies have explored whether risk factor profiles differ by the anatomic site of the cancer, which might imply different carcinogenic origins. Among these studies, most have used case-case designs in which peritoneal or fallopian tube cancer cases were compared with ovarian cancer cases,^{53–57} although several studies compared 2 or more case groups defined by site of origin with a common healthy control group,^{58,59} allowing direct comparison of odds ratios (ORs) across anatomic sites. Although results are not entirely clear, these studies suggest that associations of several established risk factors may vary by tumor site of origin such that associations with ovarian cancer are in the expected direction, whereas associations with fallopian tube and peritoneal cancers may be similar, null, or in the opposite direction.

For example, in the Australian Ovarian Cancer Study (AOCS), which included invasive serous ovarian (n = 627), peritoneal (n = 129), and fallopian tube cancer cases (N = 45) and 1508 control women, higher parity and longer duration of breastfeeding were each associated with lower risks of ovarian cancer; the associations with fallopian tube cancer were similar to those for ovarian cancer, whereas the associations with peritoneal cancer were null or attenuated.⁵⁹ In the North Carolina Ovarian Cancer Study (NCOCS), which enrolled 495 women with epithelial ovarian cancer, 62 women with primary peritoneal cancer, and 1086 control women, ORs for ever being pregnant and number of pregnancies were similarly inverse for ovarian and peritoneal cancers; however, older age at last pregnancy was associated with a decreased risk of ovarian cancer (OR, 0.58; 95% confidence interval [CI], 0.39–0.86 comparing age \geq 35 years vs <25 years), but an increased risk of peritoneal cancer (OR, 2.78; 95% CI, 1.00–7.78). Similarly, tubal ligation was associated with reduced risk of ovarian cancer but not associated with peritoneal cancer in NCOCS, although the RRs were not statistically significantly different. In AOCS, the reduction in risk caused by tubal ligation was similar across anatomic sites.⁵⁸

Given the limited the number of studies, it is difficult to conclude whether cancers at different anatomic sites should be considered distinct outcomes. Continued collaborative efforts are warranted in order to achieve an adequate sample size for continued investigation.

Tumor dominance and laterality

It is now accepted that a substantial proportion of serous tumors arise from the fallopian tubes, whereas some nonserous histologic subtypes, such as endometrioid, may arise from endometriosis or retrograde menstruation. Because ovarian cancer is usually diagnosed at a late stage when disease has spread, determining the cell of origin is often very difficult.⁴⁹ Pathology studies have suggested that dominant tumors (restricted to 1 ovary or at least twice as large on 1 ovary compared with the

other) are less likely to have a serous tubal intraepithelial carcinoma and are more likely to be of nonserous histologic subtypes, compared with those with tumor spread more evenly or diffusely across the peritoneal cavity. Further, endometriosis is often found on the left side; this may reflect greater ovulation events on the right side, leading to higher localized progesterone production, which suppresses endometriosis, as well as less efficient elimination of retrograde menstruation caused by anatomic proximity with the colon or decreased flow of peritoneal fluid on the left.³⁴ Thus, laterality of dominant tumors may be more likely to be related to this cell of origin.

Specifically, in a study of 1386 tumors, nondominant tumors were more likely to be serous and stage III/IV. In addition, nondominant tumors were associated with BRCA 1/2 mutation carrier status, higher parity, and use of estrogen hormone therapy. The association with BRCA mutations supports the now accepted theory that the distal fallopian tube is the site of high-grade serous cancers among BRCA mutation carriers.⁶⁰ In another study among 1771 patients with invasive epithelial ovarian cancer, 61% were dominant, whereas 39% were nondominant. Reproductive factors such as tubal ligation, 2 or more births, endometriosis, and age were more strongly associated with dominant tumors than nondominant tumors,⁶¹ again supporting the role of reproductive factors in tumors with a non-fallopian tube site of origin. These large studies provide provocative evidence of different developmental pathways of ovarian tumors based on a woman's risk factor profile.^{60,61}

Tumor aggressiveness

There is wide variation in length of ovarian cancer survivorship. Surveillance, Epidemiology, and End Results (SEER) data from 1998 to 2007 indicated that 47.1% of patients died of ovarian cancer within 3 years of diagnosis versus 34.1% of patients who survived longer than 10 years after diagnosis. In a combined analysis of 4 studies (2 cohort and 2 case control) with a total of 4342 ovarian cases, cases were classified as being rapidly fatal (ie, death within 3 years) or less aggressive disease (all others). Older age (positive association) and OCP use (protective association) were more strongly associated with rapidly fatal than less aggressive disease. Higher parity was only associated with a decreased risk of less aggressive disease. Results were consistent after accounting for differences in study design, geographic location, and timing across cohorts, although sparse data on tumor grade and treatment prevented rigorous consideration of these factors in analyses. Overall, these results may contribute to development of primary prevention strategies for the most aggressive cancers.³⁵

GENETIC MUTATIONS AND PREDISPOSITION

Family history remains one of the strongest risk factors for epithelial ovarian cancer. Women with a first-degree relative with ovarian cancer have a 3-fold increased risk of developing the disease compared with women with no family history. Twin studies indicate that inherited genetics are more significant than environmental and lifestyle factors.⁶² *BRCA1* and *BRCA2* gene mutations are high-penetrant susceptibility genes and the most influential predictors of inherited risk for ovarian cancer. About 15% of patients with high-grade serous epithelial ovarian cancer have a germline mutation in one of the *BRCA* genes.⁶³ Women with *BRCA* mutations almost exclusively develop serous histologic subtype disease.⁴¹ Consistent with this pattern, family histories of breast and ovarian cancer were each associated with an increased risk of serous tumors in the OC3. Family history of breast cancer was also associated with endometrioid carcinomas.³¹ The overall risk of ovarian cancer for a woman with a *BRCA1*

mutation is approximately 39% to 46% and 10% to 27% for *BRCA2* mutation carriers by age 70 years.^{64–67} In the general population, the estimated risk of carrying a *BRCA* mutation varies between 1 in 300 and 1 in 800 individuals. However, in certain populations, such as Ashkenazi Jews, the mutations are found more frequently in about 1 in 40 individuals. Risk-reducing surgery for known *BRCA* carriers by bilateral salpingo-oophorectomy has been successful in reducing epithelial ovarian cancer mortality. Typically, surgery is recommended for *BRCA1* carriers aged 35 to 40 years and *BRCA2* carriers aged 40 to 45 years, taking into account the patient's future child-bearing preferences.⁴¹

More recent evidence indicates that methylation of the *BRCA1* promoter in white blood cells (WBCs) is an additional factor influencing ovarian cancer risk. An analysis of blood samples obtained from 1541 women with ovarian cancer before chemotherapy and 3682 matched controls found that most of the women, regardless of case-control status, had normal germline *BRCA1* test results. However, 9% of women with cancer had abnormal methylation in the *BRCA1* promoter in circulating WBCs compared with 4% of control participants. After adjusting for multiple factors, the presence of methylated *BRCA1* conferred a 3-fold higher risk of ovarian cancer. If confirmed in prospective studies, systemic abnormal promoter methylation of *BRCA* could be one of the strongest known risk factors beyond germline *BRCA* mutations.⁶⁸ Further, understanding of its relationship to different histologic subtypes of disease would also elucidate the cause of ovarian carcinogenesis.

All the known susceptibility alleles that have currently been identified account for less than half of the heritable component of ovarian cancer, suggesting there are more mutations to be discovered. Although clinical management of *BRCA* mutation carriers is clear, clinical difficulties arise when counseling patients with intermediate-risk susceptibility genes. These genes include *FANCM*, *RAD51C*, *RAD51D*, *BRIP1*, and DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*). The DNA mismatch repair genes are associated with the autosomal dominant, inherited Lynch syndrome, which confers greater risk of gynecologic cancers, with endometrial cancer remaining the most common, but also an increased risk of ovarian cancer. Women with Lynch syndrome who develop ovarian cancer typically have nonserous histology with endometrioid and clear cell tumors as the most common subtypes. Epithelial ovarian cancer risk is estimated to be 4% to 20% in *MLH1* carriers, 7.5% to 20% in *MSH2* carriers, and up to 13.5% in *MSH6* carriers. *PMS2* mutations account for very few cases. Genome-wide association studies have identified 39 independent epithelial ovarian cancer risk regions, with each risk region associated with only modest increased risk. All of these alleles have been associated with high-grade serous epithelial ovarian cancer. In contrast with high-penetrant genes, most of these common variant risk alleles are located in the non-protein-coding regions of the genome, implying that epigenomic regulation of 1 or more target genes is necessary and that they are not directly involved in DNA repair.⁶³ However, OncoArray and the Collaborative Oncological Gene-Environment Study (OCAC) identified 30 epithelial ovarian cancer risk loci by genome-wide association studies and examined their associations with specific histologic subtypes. They found that *HOXD9* is a likely target susceptibility gene in both serous and mucinous histologic subtypes that also affects focal adhesion within a cancer-related pathway. *HNF1B* was downregulated in most serous ovarian cancers, but overexpressed in clear cell ovarian carcinomas.⁶⁹ Histologic subtype-specific studies such as this one will help further the understanding of risk reduction given the heterogeneity of ovarian cancer.

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